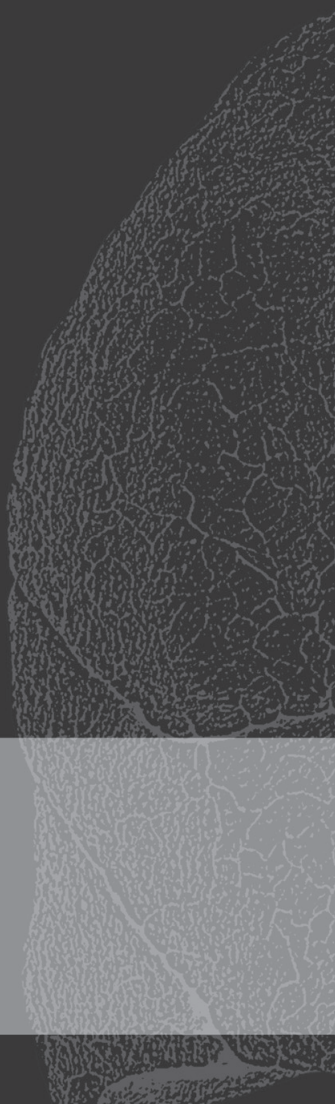
Brain metastases in lung cancer patients

Valorization



VALORIZATION

In 2013 in the Netherlands, 12,660 patients were diagnosed with lung cancer.[1] Approximately 30% was diagnosed in a locally advanced state (*i.e.* stage III) and 50% in an already metastatic state (stage IV).[2] Non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) account for 80-85% and 15-20% of lung cancer cases, respectively.[3] Approximately 40% of lung cancer patients will develop brain metastases during the course of their disease.[4] These brain metastases often have a negative impact on quality of life (QoL).[5] In this thesis we tried to unravel clinical questions regarding screening, prevention and treatment of brain metastases. As a result of the scientific content of this thesis several recommendations have been made in chapter 11. However, besides a scientific analysis of these studies, there are some socio-economical applications and the possibility to develop clinical decision aid tools.

The percentage of the "Gross Domestic Product" spend on health care in the Netherlands is approximately 14% and is still increasing.[6] From an economical point of view, the results described in this thesis can aid in reducing the costs of treating lung cancer patients in several possible ways. Examples are omitting unnecessary imaging procedures (brain magnetic resonance imaging (MRI) in stage III NSCLC), omitting end-of-life-whole brain radiotherapy (WBRT) and using population based databases for prognostic information and concepts for validation in future studies.

The first to be discussed is the MRI of the brain in neurologically asymptomatic stage III NSCLC patients. Depending on the specific MRI protocol and the hospital, one brain MRI costs around 300-400 euros. In the Netherlands, approximately 3000 patients per year are diagnosed with stage III NSCLC . Depending on clinical condition, comorbidities and patient's wishes, these patients are candidates for therapy with curative intent. As brain MRI was found to be only marginally superior to a dedicated computed tomography (CT) of the brain, a significant amount of money can be saved by omitting a brain MRI in every stage III NSCLC patient staged with ^{18}fluorodeoxyglucose-positron emission tomography contrast-enhanced CT (^{18}FDG-PET-CE-CT). Moreover, as timely access to MRI was difficult for the participating hospitals, time to start of treatment can also be shortened by omitting a brain MRI. Problems with timely access to MRI are not unique for the participating hospitals, as in a United Kingdom survey (2014) CE-CT was preferred above MRI, presumably due to lack of access to MRI.[7]

The second example to reduce health care costs is the prevention of end-of-life-WBRT. For one patient, WBRT costs are € 9886.01 (MAASTRO data).[8] In general, it is advised to withhold active treatment in patients with a very poor prognosis and to pursue only optimal supportive care as these patients do not benefit from active treatment.[9] This thesis describes the results of a large group of lung cancer patients diagnosed with brain metastases and treated with WBRT. As is shown, the overall survival in the recursive partitioning analysis (RPA) class III group is dismal and no prognostic factors could be identified that were associated with an improved survival. Moreover, in the

QUARTZ study, it was shown that omitting WBRT in a poor prognosis group does not harm patients.[10]
The third example is the use of population based databases. Clinical trials are becoming more and more expensive and it is not always clear whether results found within a clinical trial / registry based on data from selected patients treated at a referral center can be extrapolated to the general population. Population based registries, like we have used in chapter five can aid in validating clinical trial results or providing data for future clinical trials without additional costs. For example, number of organs with metastases could be used to stratify patients in clinical trials. Furthermore, the concept of oligometastatic disease should be further explored especially in the patients with a low local disease status as we have described that these patients have the best survival. Population based results can also provide prognostic factors such as the ones described above. These factors should be validated in the 9th tumour, node, metastasis (TNM) classification for lung cancer.

This thesis has also some social implications. An example is that it should not matter in which hospital in a certain region a patient is diagnosed with lung cancer: work-up and treatment should not be different. However, as is clear from chapter three, chemotherapy regimens within a chemoradiotherapy regimen vary widely across hospitals. There are no head to head clinical trials comparing these regimens, but from published clinical trials it seems that there is no superior one.[11] Moreover, we have shown that there is no impact of the chemotherapy used on the diagnosis of brain metastases after treatment completion. As there are no significant differences for these regimens (also no difference for overall survival), this thesis provides evidence to adopt one single regimen within the Netherlands. This would also prevent miscommunication with referred patients because of different treatment regimens applied in different hospitals. Moreover, there is no consensus whether NSCLC patients with a driver mutation, treated with a tyrosine kinase inhibitor (TKI) and diagnosed with brain metastases, can be treated with cranial irradiation concurrent with the TKI. In a short survey among pulmonologists and radiation oncologists, practice varied between continuation of the TKI, discontinuation of the TKI only for the days of cranial irradiation to discontinuation of the TKI for five half-times before and after the cranial irradiation (personal communication). This thesis provides evidence that it is safe to combine a first generation epidermal growth factor receptor (EGFR)-TKI and WBRT. These data also provide evidence that can be used in a new guideline on cranial radiotherapy concurrent with systemic treatment.
Another social aspect is that cancer patients do not want to lose hope. However, sometimes the definition of hope needs to be rephrased, *e.g.* in poor prognosis lung cancer patients diagnosed with brain metastases.[12] By focusing on offered treatments the patients and physicians often ignore the dismal future due to a focus on short-term goals (*e.g.* make it to the next treatment or test.[13] Moreover, in a survey supportive

care was often not viewed as a real alternative compared to active treatment.[12] Possibly a team-based consult service through a multidisciplinary integrated palliative oncology clinic would have improved this decision making process as was shown in a recent study.[12] The results described in this thesis provide additional grounds to have such a multidisciplinary approach including physician and patient education in every hospital as it seems that the prognosis of the RPA class III patients was overestimated. Another translational of these results would be the development of a clinical decision aid.

This thesis can also aid in improving the ongoing revision of the Dutch guideline on brain metastases. Examples already mentioned are the value of MRI in diagnosing asymptomatic brain metastases in stage III NSCLC and omitting end-of-life-WBRT in poor prognosis brain metastases patients. However, more factors should be taken into account when deciding whether a patient is eligible for cranial radiotherapy and this should be described in the revised guideline. Prognostic examples found in this thesis are the presence or absence of extracranial metastases and number of organs with metastases. Furthermore, today it is not taken into account whether an effective systemic treatment is available for the extracranial disease (especially first line chemotherapy for small cell lung cancer (SCLC) and TKIs for patients with molecular drivers, but in a lesser extent also first line chemotherapy for NSCLC) and whether this systemic treatment also penetrates the (compromised) blood-brain barrier (BBB) to also have an effect on the brain metastases. Ideally, prognostic classification, patient preferences, available systemic options and patient outcome (symptoms and survival) should be incorporated into the guidelines and preferably into a decision aid that continues to improve by the input it receives.
In conclusion, this thesis has a socio-economical relevance and provides opportunities to develop decision support tools. The economical relevance is demonstrated by possibilities to reduce costs by sometimes omitting imaging and by omitting end-of-life WBRT. The social relevance comes from described possibilities to make uniform treatment decisions (chemotherapy regimens within a chemoradiotherapy regimen, TKI concurrent with WBRT) and education of physicians and patients about poor prognosis in RPA class III patients. It also provides opportunities to develop new clinical decision aid tools and might have impact on the revision of the Dutch guideline on brain metastases from solid tumours.

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